REMARKS

Claims 1, 2, 7 and 8 were pending. Claims 13-16 have been added. Therefore, claims 1, 2, 7, 8, and 13-16 will be pending upon entry of the present amendment.

No new matter has been added. Support for new claims 13-16 can be found in the specification as originally filed, for example, at least at page 8, line 12; page 9, line 11; page 13, lines 21-22; and page 17, lines 1-8.

Applicants would like to thank the Examiner for meeting with Applicants' attorneys on May 14, 2007.

Rejection of Claims 1, 2, 7 and 8 under 35 U.S.C. § 103(a)

Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jennings (WO 094/17794), in view of Coffin (U.S. 5,492,930). Applicants respectfully traverse this rejection.

Applicants' claims are directed to methods of treating a subject afflicted with amyotrophic lateral sclerosis, by administering to the subject an amount of creatine or creatine phosphate.

According to the Examiner, Jennings describes "compositions comprising amounts of creatine and creatine phosphate for use in treating wasting diseases." Jennings describes the use of compositions comprising a sugar and glycine derivatives to enhance cardiac tissue formation. Jennings does not teach or suggest the use of creatine or creatine phosphate to treat amyotrophic lateral sclerosis, as claimed by Applicants.

Coffin fails to overcome the deficiencies of Jennings. Coffin is directed to a method for treating central nervous system disorders and improving cognitive ability in mammals, by using 2-phenyl-1,3-propanediol monocarbamate-not creatine or creatine phosphate. In fact, Coffin does not even describe the use of 2-phenyl-1,3-propanediol monocarbamate to treat amyotrophic lateral sclerosis. ALS is only mentioned in the background section when describing the teachings of a prior art publication, EP 0 531 105 A1. This publication describes the use of felbamate for treating "Guam ALS, Parkinson's disease, Alzheimer's disease, dementia and lathrism." Coffin distinguishes his compound, 2-phenyl-1,3-propanediol monocarbamate over felbamate by stating that it has a different physiological effect than felbamate and "its action is uniquely different from felbamate."

An ordinarily skilled artisan would not have been motivated to combine the teachings of Coffin with Jennings because one of ordinary skill in the art would appreciate that each disease has unique characteristics. One of ordinary skill in the art would not be motivated to combine the teachings of Jennings and Coffin because an

ordinarily skilled artisan would have no expectation of success. While Coffin teaches that to treat certain neurodegenerative disorders it may be useful to reverse deficits resulting from a loss of cholinergic or NMDA receptor function, there is no teaching or suggestion in Jennings that creatine or creatine phosphate fulfills this role or would treat the disease.

In addition, Applicants submit that creatine has been shown to work surprisingly well in the treatment of amyotrophic lateral sclerosis. As described in the declaration of Belinda Tsao Nivaggioli, Ph.D., creatine has been shown to extend the survival time of amyotrophic lateral sclerosis patients by approximately four years.

Declaration

The attached declaration of Dr. Nivaggioli presented data which shows that creatine works surprisingly well in the treatment of amyotrophic lateral sclerosis.

In particular, the declaration describes an analysis of two placebo-controlled randomized trials. In these trials, five grams of creatine were administered per day to subjects suffering from amyotrophic lateral sclerosis. The trials included a total of 211 patients, including 103 creatine-treated and 108 placebo-treated patients.

To analyze the data, a measure of treatment effect in an estimated pooled hazard ratio was calculated. This measure gave the risk of death for treated subjects divided by the risk of death for controls. Survival analysis by treatment was also performed for each trial separately. A Cox model was used to assess the hazard ratios and survival by treatment in the pooled data, controlling for trial effect and baseline variables. Baseline characteristics of the study populations were also compared. Continuous variables were compared by treatment and trial, using the analysis of variance by putting both treatment and trial as the dependent variables. A Cochran-Mantel-Haenszel test statistic was used to compare discrete variables by treatment and trial, controlling for trial and treatment effects, respectively.

Five grams of creatine per day improved survival in the pooled data. The adjusted hazard ratio was 0.34 (95% confidence interval 0.11 to 1.04) for the creatine group relative to the placebo group. Median survival showed a two-to-three-fold improvement for subjects taking creatine over placebo (87 months compared to 27 months). The effect was homogeneous between trials ($p=0.062$, hazard ratio 0.34, 95% confidence interval 0.11 to 1.06), suggesting no major differences in survival due to subject variables. Figure 1 shows the survival analysis for each trial and pooled data. This analysis shows that creatine 5 grams daily prolongs median survival time in subjects with amyotrophic lateral sclerosis.

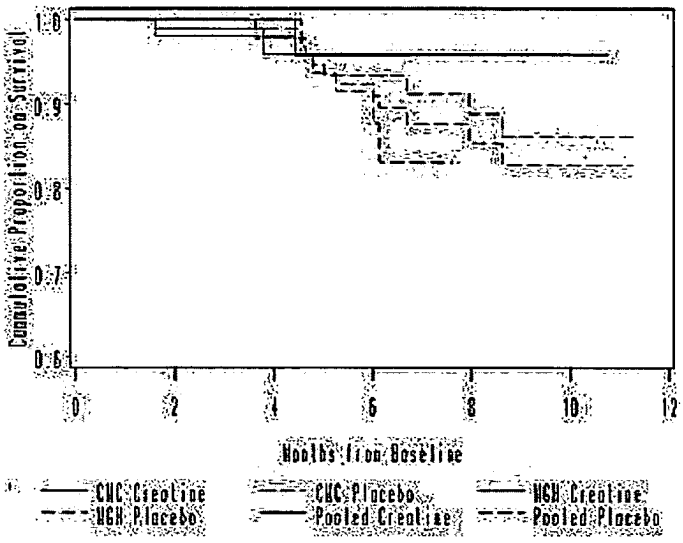

Figure 1

Median survivals were also calculated. The median survival is the number of months 50% of the patients would have survived in each treatment arm. Since only a small percentage of patients died during the 8-11 month of study period, the median survival is statically calculated to project to the point where 50% of the patients would have died. Figure 2, below, shows that the median survival time of the subjects treated with creatine increased from 27 months to 87 months.

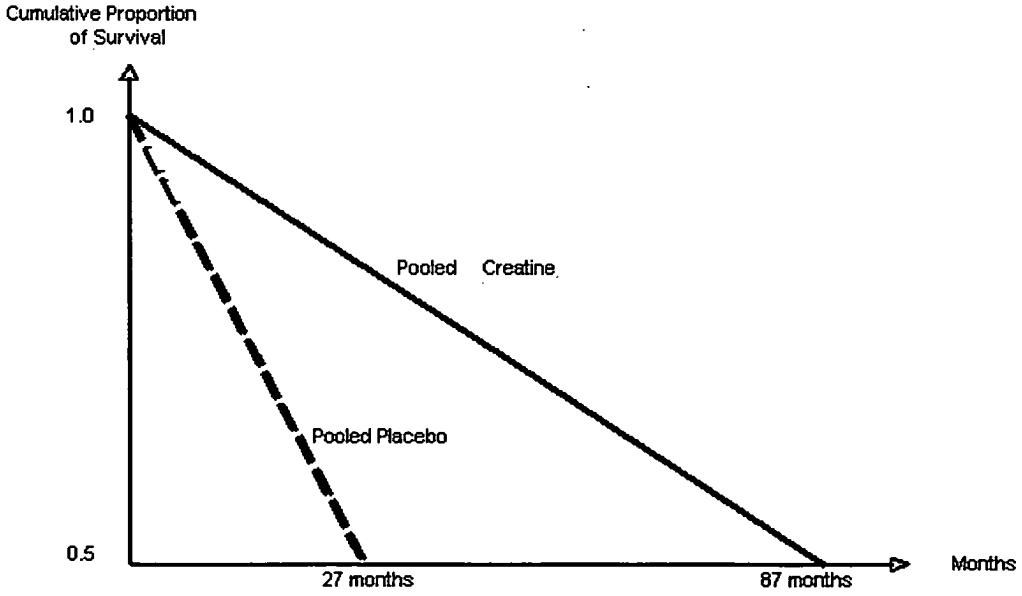

Figure 2

In contrast to creatine which extends the average survival time of subjects with ALS about fifty months (approximately four years), treatment with Riluzole (the FDA approved amyotrophic lateral sclerosis drug) only extends average survival time approximately two to three months (Miller, R.G. *et al.*, Cochrane Database Syst Rev. 2002;(2):CD001447).

For at least the above reasons, creatine has surprising and unexpected therapeutic activity for the treatment of amyotrophic lateral sclerosis. This surprising activity is not taught or suggested by the prior art. Therefore, Applicants respectfully request that this rejection of claims 1, 2, 7, and 8 under 35 U.S.C. § 103 (a) be reconsidered and withdrawn.

Rejection of Claims 1, 2, 7 and 8 under 35 U.S.C. § 103(a)

Claims 1, 2, 7 and 8 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over Jennings (WO 094/17794), in view of Flohe (U.S. 4,788,179). Applicants respectfully traverse this rejection.

Applicants' claims and Jennings are described above.

Flohe is directed to the use of dipeptide compounds for the treatment of amyotrophic lateral sclerosis. Flohe does not teach or suggest the use of creatine nor creatine phosphate for the treatment of amyotrophic lateral sclerosis. According to the Examiner, Flohe "teaches the use of a peptide mendicant that resulted in an improvement of muscle weakness in an ALS patient." Flohe notes that in ALS "the patient's intellect remains clear."

The present invention would not have been obvious to an ordinarily skilled artisan in view of Jennings and Flohe. Jennings is directed to enhancing cardiac tissue formation for patients suffering from dementias. Jennings does not teach or suggest methods for treating ALS, let alone treating ALS with creatine or creatine phosphate, as claimed by Applicants.

Flohe fails to overcome the deficiencies of Jennings. In particular, Flohe merely teaches the use of dipeptide derivatives for the treatment of ALS, and does not teach or suggest the use of creatine or creatine phosphate. An ordinarily skilled artisan would not be motivated to combine the teachings of Flohe with the teachings of Jennings because the teachings of Flohe are directed to the use of a particular class of compounds, which does not include creatine nor creatine phosphate. While Flohe noted that there was some improvement in muscle weakness when the dipeptide compounds were administered, an ordinarily skilled artisan would appreciate that these observations would pertain only to

the compounds actually tested and claimed by Flohe. Furthermore, one of ordinary skill in the art would also appreciate that the improvement in muscle weakness may be indicative of an improvement in the rate of neurodegeneration and not simply and improvement in one symptom. Jennings merely teaches that combinations of creatine and sugar may be useful for enhancing tissue formation. It would not be obvious to one of ordinary skill in the art that these compounds could be used to treat amyotrophic lateral sclerosis, merely because the compounds described are alleged to treat one symptom of the disease.

Furthermore, as described above, Applicants submit herewith a declaration of Dr. Nivaggioli which presents data which shows that creatine has unexpected and surprising activity for the treatment of amyotrophic lateral sclerosis. This surprising activity is not taught or suggested by the prior art.

Therefore, Applicants respectfully request that this rejection of the claims under 35 U.S.C. § 103 (a) be withdrawn.

Provisional Rejection of Claims 1, 2, 7 and 8 under Non-Statutory Obviousness Type Double Patenting

Claims 1, 2, 7, and 8 have been provisionally rejected under non-statutory obviousness type double patenting over claims 1-4, 7,8 and 13 of copending application 10/718,765.

While in no way admitting that the present claims are obvious over claims 1-4, 7,8 and 13 of copending application 10/718,765, upon allowance of the '846 application, Applicants will consider submitting a terminal disclaimer in compliance with 37 C.F.R. 1.321(b) and (c), if appropriate, which will obviate the rejection.

SUMMARY

In view of the remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

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